CHAPTER 11 – Investigational Drugs, Agents, Biologics, and Devices

Investigational Drugs/Investigational Biologics (Test Articles)
A new drug/agent or biologic that is used in a clinical investigation. The term investigational biologic also includes a biological product that is used in vitro for diagnostic purposes. Investigational drugs or biologics may include:

A. Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA; or

B. Products already approved by the FDA as safe and effective for specific indications that are being studied for new indications (or doses, strengths, or frequency).

Researchers who employ a test article classified by the Food and Drug Administration as an investigational new drug must comply with the FDA's IND regulations (21 CFR 312). The IND number assigned to the test article must be filed with the IRB when the application for review is submitted. See policy 33 for additional information about INDs.

Storage of Investigational Drugs/Devices
It is the policy of the ETSU/VA IRB that all investigational drugs, devices, drugs, or biologics used in human subject research be stored, handled and dispensed in accordance with governing regulations and institutional policy. It is the responsibility of the investigator to comply with all institutional, state, and federal regulations in regards to storage of investigational drugs, agents, or biologics.

VA/MSHA
All research investigators conducting VA approved human subjects research protocols involving the use of pharmaceutical agents must be in compliance with all VHA policies/handbooks as they relate to obtaining, prescribing, and the storing of pharmaceuticals as well as addressing required record keeping. In addition, investigators using any controlled substances including Schedule II and III narcotics must be in full compliance with VHA Pharmacy Policies and Drug Enforcement Administration (DEA) Regulations. If the use of pharmaceuticals is covered under FDA Regulations, those regulations must be followed as well.

VA researchers are responsible to ensure the local Pharmacy Service or Research Service Investigational Pharmacy receives:

⇒ Documentation of IRB and any other relevant approvals.
⇒ A copy of VA Form 10-9012 (if applicable).
⇒ A copy of the current approval protocol.
⇒ A copy of the consent document for each participating participant with all appropriate signatures.
⇒ Documentation of IRB continuing review approval.
⇒ Copies of sponsor-related correspondence specific to the drugs as appropriate.
⇒ Copies of all correspondence addressed to the Researcher from the FDA specific to the investigational drugs as appropriate.
⇒ Inform the chief, pharmacy service, the research pharmacy when applicable, and the Research Development Committee and the IRB in writing with a study involving investigational drugs has been suspended, terminated, or closed.
⇒ Comply with all dispensing requirements.
⇒ Comply with all documentation requirements and make relevant records accessible to the investigational drug pharmacist when requested.

In addition, studies conducted at Mountain States Health Alliance must follow all applicable MSHA policies.

Controlled substances may not be stored outside of the pharmacy department of the involved hospital.

**PI Responsibilities Summary**


The PI is responsible for assuring the IRB that investigational drugs and devices are stored in a secure and safe manner and that the storage and safety requirements are consistent with FDA, sponsor, and affiliated research institutions’ storage requirements for drugs or devices being investigated. Whenever possible, the storage of drugs and biologics should be under the supervision of a registered pharmacist and stored in the pharmacy in a limited access, locked area. Devices should be stored according to manufacturer’s specifications and maintained in a limited access area. Access to the test device must be limited only to those authorized to use the devices.

The PI is responsible for ensuring that test articles (drugs, biologics, or devices) are controlled so that they are not used outside of a research study. An investigator shall administer the drug or device only to subjects under the PI’s personal supervision or under the supervision of a sub-investigator responsible to the PI. The PI shall not supply the investigational drug or device to any person not authorized to receive it.

The protocol for the study should outline the security and storage plan for the test article(s) indicating that the plan meets the sponsor’s storage and security requirements. The plan should include whether or not control will be through a hospital pharmacy and under the supervision of a registered pharmacist or held in a proper and secure storage area by the investigator. The protocol should detail how the test article is used in human subjects, indicate who may have access to the test article(s) and outline the accountability plan for the test article(s) to ensure that there is no unapproved access to or use of the test article(s).
PI responsibilities related to investigational drugs are outlined in the supplemental section for drugs embedded in the new protocol submission xForms. This section is required for submission for investigational drug studies. PI responsibilities related to investigational devices are outlined in the supplemental section for devices in the new protocol submission xForms. This section is required for submission for investigational device studies.

**Additional Responsibilities for PI Acting as Sponsor**

If a PI is acting as the sponsor of research involving an investigational drug, the ETSU/VA IRB requires that the PI submit documentation that the proposed drug preparation has been reviewed and determined to be in compliance with Current Good Manufacturing Practices. In addition, when an PI is acting as the sponsor of research involving an investigational drug or device, the IRB requires that the PI review the reporting and record-keeping responsibilities as stated in 21 CFR 312 and 21 CFR 314 (for investigational drugs) or 21 CFR 812 and 21 CFR 814 (for investigational devices). (Also see policy 33)

**Medical Investigational Device Determinations**

A Significant Risk (SR) device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study.

NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

In reviewing studies involving medical devices, the Medical Campus ETSU/VA IRB will make two determinations:

- Whether a device study represents a significant or non-significant risk; and
- Whether the study should be approved.

These questions will be considered separately because the issues involved in making these decisions are quite different. Determining whether a device study poses a significant risk will be based solely on considerations of risk to subjects, while the IRB approval of the study is based on many factors. In determining whether a device study presents a significant or non-significant risk, both the risk of the device and the risk associated with the procedure for using the device (e.g., surgery for installing an implant) will be considered. The comparison of risks will provide the basis for whether or not the IRB will approve the research.

The initial assessment of whether or not a device study presents a non-significant risk (NSR) is made by the sponsor.
In addition to receiving a completed Form 103, narrative, informed consent, protocol and investigator’s brochure (if available), the IRB must receive a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The IRB must also be informed whether other IRBs have reviewed the proposed study, and what determinations were made. In addition, the IRB must be informed of the FDA’s assessment of the device’s risk if such an assessment has been made. If the sponsor considers that a study is NSR, the sponsor must provide the IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor must provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

For any device protocol considered (by FDA) to present significant risk, an IDE number will be required prior to submission to the ETSU/VA IRB for initial review. Conversely, if the FDA has made a determination of non-significant risk, than a copy of the determination letter received from FDA should be submitted with the protocol.

The IRB may also consult with FDA for its opinion. The IRB uses its expertise, information in the FDA regulations and guidelines, and the risk evaluation provided in the application to determine the risk category.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA.

If the IRB disagrees and determines that the device is SR, the IRB informs the investigator and the sponsor in writing of this decision and its basis. The sponsor should notify FDA that an SR determination has been made. If the IRB determines that a device study is SR, the study may not begin until both the IRB and FDA approve the investigation. The study can be conducted as an SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, the IRB considers the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the participant must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB considers the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR.

If the investigator or organization is acting as the sponsor, the investigator or sponsor must follow all the additional regulatory requirements of sponsors. The IRB must evaluate whether the investigator knows how to follow the additional regulatory requirements of sponsors. In order to determine this evaluation, the IRB requires any investigator acting as the sponsor to read the FDA’s “Responsibilities for Sponsors of Significant Risk Device Studies,
Responsibilities for Sponsors of Non-Significant Risk Device Studies”, “Responsibilities for Investigators of Significant Risk Device Studies, Responsibilities for Investigators of Non-Significant Risk Device Studies” published on-line at http://www.fda.gov/cdrh/devadvice/ide/print/responsibilities.html. The IRB receives a signed attestation that the investigator/sponsor has read this document prior to issuing final study approval.